10/806,972 Reconsidered Updated Search 1/23/07 BP

intramuscular, intrasphincter, oral or parenteral) to achieve a comparable suppressant effect.

7. the suppressant effects of the present methods can result in the desirable side effects of greater patient mobility, a more positive attitude, and an improved quality of life.

8. high, therapeutic doses of a neurotoxin can be delivered to an intracranial target tissue over a prolonged period without systemic toxicity.

Although the present invention has been described in detail with regard to certain preferred methods, other embodiments, versions, and modifications within the scope of the present invention are possible. For example, a wide variety of neurotoxins can be effectively used in the methods of the present invention. Additionally, the present invention includes intracranial administration methods wherein two or more neurotoxins, such as two or more botulinum toxins, are administered concurrently or consecutively. For example, botulinum toxin type A can be administered intracranially until a loss of clinical response or neutralizing antibodies develop, followed by administration of botulinum toxin type B. Furthermore, non-neurotoxin compounds can be intracranially administered prior to, concurrently with or subsequent to administration of the neurotoxin to provide adjunct effect such as enhanced or a more rapid onset of suppression before the neurotoxin, such as a botulinum toxin, begins to exert its more long lasting suppressant effect.

My invention also includes within its scope the use of a neurotoxin, such as a botulinum toxin, in the preparation of a medicament for the treatment of a neuropsychiatric disorder, by intracranial administration of the neurotoxin.

All references, articles, patents, applications and publications set forth above are incorporated herein by reference in their entireties.

Accordingly, the spirit and scope of the following claims should not be limited to the descriptions of the preferred embodiments set forth above.

I claim:

1. A method for alleviating a symptom of a neuropsychiatric disorder, the method comprising the step of administering to a patient with a symptom of a neuropsychiatric disorder a therapeutically effective amount of a Clostridial neurotoxin, wherein the Clostridial neurotoxin is administered to an intracranial site which is associated with the symptom of the neuropsychiatric disorder, thereby alleviating the symptom of the neuropsychiatric disorder, wherein the Clostridial neurotoxin is administered to an intracranial site selected from the group of intracranial sites consisting of a locus cerulcus and a ventral tegmental area.

2. The method of claim **1**, wherein the neurotoxin is made by a bacterium selected from the group consisting of *Clostridium botulinum, Clostridium butyricum* and *Clostridium beratti.*

3. The method of claim **1**, wherein the neurotoxin is a botulinum toxin.

4. The method of claim **3**, wherein the botulinum toxin is selected from the group consisting of botulinum toxin types A, B, C_1, D, E, F and G.

5. The method of claim **3**, wherein the botulinum toxin is botulinum toxin type A.

6. The method of claim **3**, wherein the botulinum toxin is administered in an amount of between about 10^{-4} U/kg and about 1 U/kg.

7. The method of claim **1**, wherein the symptom alleviating effect persists for between about 1 month and about 5 years.

8. The method of claim **1**, wherein the Clostridial neurotoxin is a recombinantly produced Clostridial neurotoxin.

9. The method of claim **1**, wherein the intracranial administration step comprises implantation of a botulinum toxin containing controlled release system.

10. The method of claim **1**, wherein the administration of the neurotoxin alleviates a symptom of the neuropsychiatric disorder that is associated with hyperactive neurotransmitter release from neurons.

11. The method of claim **1**, wherein administering the Clostridial neurotoxin restores a balance between at least two neuronal systems that release different neurotransmitters, thereby alleviating the symptom of the neuropsychiatric disorder.

12. The method of claim **1**, wherein administering the Clostridial neurotoxin decreases an acetylcholine release from a cholinergic neuron, thereby alleviating the symptom of the neuropsychiatric disorder.

13. The method of claim **11**, wherein administering the Clostridial neurotoxin decreases a dopamine release from a dopaminergic neuron, thereby alleviating the symptom of the neuropsychiatric disorder.

14. The method of claim **1**, wherein administering of the Clostridial neurotoxin decreases a norepinephrine release from a noradrenergic neuron, thereby alleviating the symptom of the neuropsychiatric disorder.

15. A method for treating a symptom of a neuropsychiatric disorder, the method comprising the step of administering to a patient with a symptom of a neuropsychiatric disorder a therapeutically effective amount of a botulinum toxin, wherein the botulinum toxin is administered to an intracranial site which is associated with the symptom of the neuropsychiatric disorder, thereby treating the symptom of the neuropsychiatric disorder, wherein the botulinum toxin is administered to an intracranial site selected from the group of intracranial sites consisting of a locus ceruleus and a ventral tegmental area.

16. The method of claim **15**, wherein the botulinum toxin is botulinum toxin type A.

17. The method of claim **15**, wherein the neuropsychiatric disorder is selected from the group consisting of schizophrenia, Alzheimer's disease, mania, and anxiety.

18. A method for treating of a neuropsychiatric disorder, the method comprising the step of administering to a patient with a symptom of a neuropsychiatric disorder a therapeutically effective amount of a botulinum toxin, wherein the botulinum toxin is administered to an intracranial site which is associated with the symptom of the neuropsychiatric disorder, thereby treating the symptom of the neuropsychiatric disorder by reducing neurotransmitter release from neurons contributing to the symptom of the neuropsychiatric disorder within about four months after the administration of the botulinum toxin, wherein the botulinum toxin is administered to an intracranial site selected from the group of intracranial sites consisting of a locus cerulcus and a ventral tegmental area.

19. A method for treating schizophrenia, the method comprising a step of administering to a patient with schizophrenia a therapeutically effective amount of a botulinum toxin, wherein the botulinum toxin is administered to an intracranial site which is associated with a symptom of schizophrenia, thereby treating schizophrenia, wherein the botulinum toxin is administered to an intracranial site selected from the group of intracranial sites consisting of a pedunculopontine nucleus, a locus ceruleus and a ventral tegmental area.

20. The method of claim **19**, wherein the botulinum toxin is botulinum toxin type A.

21. A method for treating schizophrenia the method comprising a step of administering a therapeutically effective amount of a botulinum toxin to a pedunculopontine nucleus of the brain of a patient with schizophrenia, thereby treating schizophrenia.

* * * * *

[0077] Methods for treating neuropsychiatric disorders comprise the step of intracranially administering a neurotoxin to a patient. The neurotoxin is administered in a therapeutically effective amount **to alleviate at least one symptom of the disorder**. The neurotoxin alleviates the symptoms associated with the disorder by reducing secretions of neurotransmitter from the neurons exposed to the neurotoxin.

Example 2

[0115] Treatment of Schizophrenia With Botulinum Toxin Type A

[0116] A 48 year old male presents with reduced motivation and interest in daily life. The patient indicates that he hears voices. The patient is monitored regularly for six months. The symptoms gradually worsen throughout the monitoring period, and the patient is diagnosed with schizophrenia. Using CAT scan or MRI assisted stereotaxis, as set forth in Example 1 above, 2 units of a botulinum toxin type A (such as BOTOX.RTM. or about 8 units of Dysport.RTM.) is injected into the pedunculopontine nucleus. The patient is discharged within 48 hours and with a few (1-7) days **enjoys significant improvement of the positive symptoms of schizophrenia. The positive symptoms of schizophrenia remain significantly alleviated for between about 2 to about 6 months**. For extended therapeutic relief, one or more polymeric implants incorporating a suitable quantity of a botulinum toxin type A can be placed at the target tissue site.

Example 3

[0117] Treatment of Schizophrenia With Botulinum Toxin Type B

[0118] A 68 year female previously diagnosed and treated for schizophrenia wishes to try a new therapeutic treatment. She seeks the advice of a physician who recommends botulinum toxin therapy. Using CAT scan or MRI assisted stereotaxis, as set forth in Example 1 above, from 10 to about 50 units of a

botulinum toxin type B preparation (such as Neurobloc.RTM. or Innervate.TM.) is injected into the pedunculopontine nuclei. The patient is discharged within 48 hours and with a few (1-7) days **enjoys significant improvement of the positive symptoms. Her hallucinations almost completely disappear. The positive symptoms remain significantly alleviated for between about 2 to about 6 months**. For extended therapeutic relief, one or more polymeric implants incorporating a suitable quantity of a botulinum toxin type B can be placed at the target tissue site.

Example 4

[0119] Treatment of Schizophrenia With Botulinum Toxin Types C.sub.1-G

[0120] A female aged 71 is admitted with disorder thought patterns and suffering from auditory and visual hallucinations. From 0.1 to 100 units of a botulinum toxin type C.sub.1, D, E, F or G is injected pedunculopontine nuclei to chemically denervate the excitatory cholinergic projection to the ventral tegmental area. CAT scan or MRI assisted stereotaxis, as set forth in Example 1 above, supplemented by ventriculography is used. The patient is discharged within 48 hours and with a few (1-7) **days enjoys significant remission of tremors which remain significantly alleviated for between about 2 to about 6 months**. For extended therapeutic relief, one or more polymeric implants incorporating a suitable quantity of a botulinum toxin type C.sub.1, D, E, F or G can be placed at the target tissue site.

[0006] Schizophrenia

[0007] Schizophrenia is a disorder that affects about one percent of the world population. Three general symptoms of schizophrenia are often referred to as positive symptoms, negative symptoms, and disorganized symptoms. Positive symptoms may include delusions (abnormal beliefs), hallucinations (abnormal

perceptions), and disorganized thinking. Hallucinations may be auditory, visual, olfactory, or tactile.

[0008] Disorganized thinking may manifest itself in schizophrenic patients by disjointed speech and the inability to maintain logical thought processes. Negative symptoms may represent the absence of normal behavior. Negative symptoms include emotional flatness or lack of expression and may be characterized by social withdrawal, reduced energy, reduced motivation, and reduced activity. Catatonia may also be associated with negative symptoms of schizophrenia. The symptoms of schizophrenia should continuously persist for a duration of about six months in order for the patient to be diagnosed as schizophrenic. Based on the types of symptoms a patient reveals, schizophrenia may be categorized into subtypes including catatonic schizophrenia, paranoid schizophrenia, and disorganized schizophrenia.

[0009] The brains of schizophrenic patients are often characterized by enlarged lateral ventricles, which may be associated with a reduction of the hippocampus and an enhancement in the size of the basal ganglia. Schizophrenic patients may also have enlarged third ventricles and widening of sulci. These anatomical characterizations point to a reduction in cortical tissue.

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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 17500CON (BOT)

In re Application of: Stephen Donovan

Application No.: 10/806,972

Filed: 03/22/2004

For: Botulinum Toxin Therapy for Neuropsychiatric Disorders

The owner*, Allergan, Inc, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term **prior patent** No. 6,921,538 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said **prior patent** is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
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2. ☑ The undersigned is an attorney or agent of record. Reg. No. 33,433

Signature — Date: 9/28/06

Stephen Donovan
Typed or printed name

714-246-4026
Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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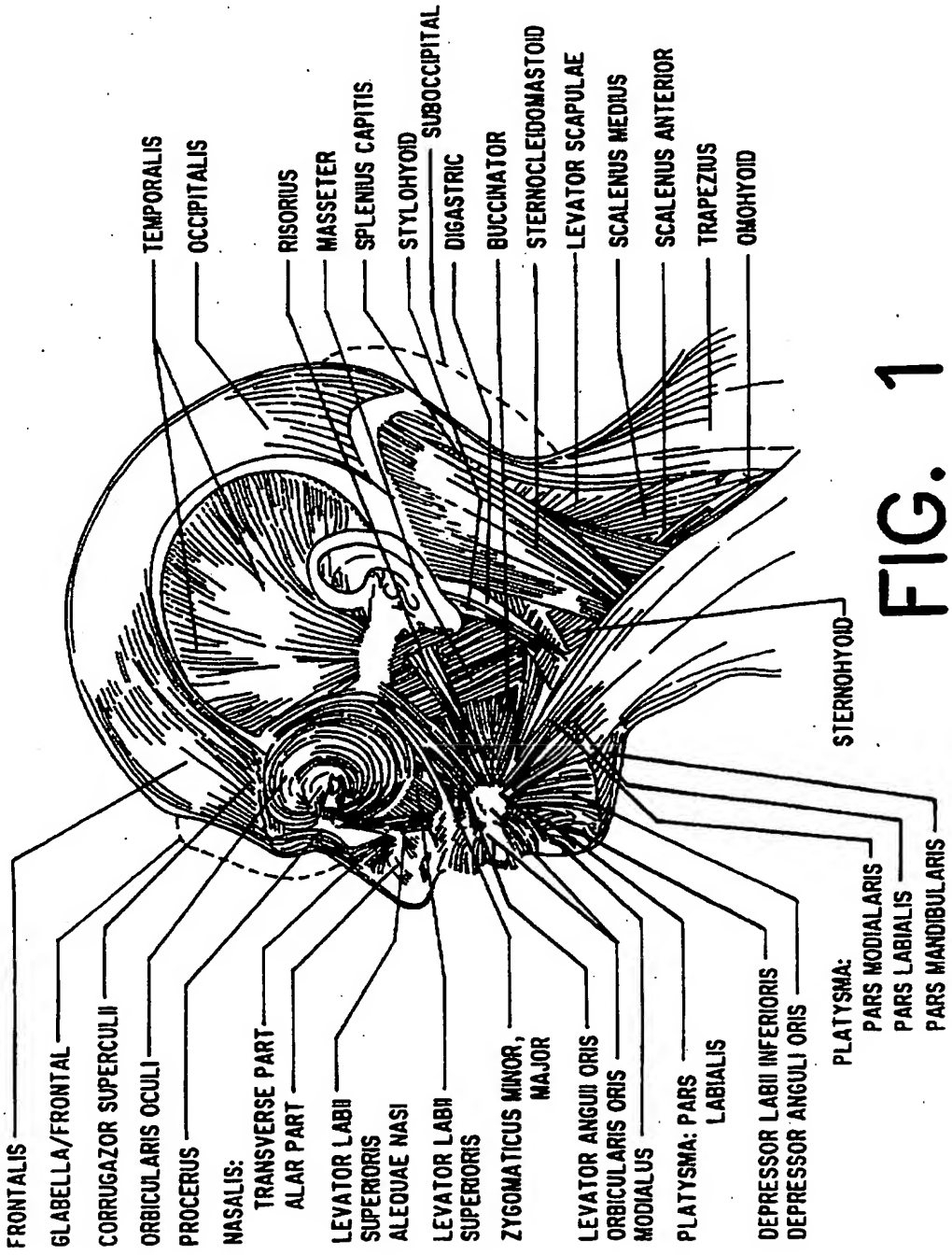
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SUPERIORIS
ALEQUAE NASI
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SUPERIORIS
ZYGOMATICUS MINOR,
MAJOR
LEVATOR ANGULI ORIS
ORBICULARIS ORIS
MODIALUS
PLATYSMA: PARS
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PARS LABIALIS
PARS MANDIBULARIS
STERNOHYOID
TEMPORALIS
OCCIPITALIS
RISORIUS
MASSETER
SPLENIUS CAPITIS
STYLOHYOID
SUBOCCIPITAL
DIGASTRIC
BUCCINATOR
STERNOCLEIDOMASTOID
LEVATOR SCAPULAE
SCALENUS MEDIUS
SCALENUS ANTERIOR
TRAPEZIUS
OMOHYOID

FIG. 1

pontine

pon·tine [pón tīn, pón teen]

adjective

Definition:

of brain nerve fibers: relating to or situated in the whitish band of nerve fibers **pons** on the surface of the brainstem between the medulla oblongata and midbrain

[Late 19th century. < Latin *pont-* "bridge, way"]